Bridging the Dimensions:
Seamless Integration of 3D Structure-based Design and 2D Structure-activity Relationships to Guide Medicinal Chemistry

ACS Spring National Meeting. COMP, March 13th 2016

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Overview

- 2-dimensional (2D) structure-activity relationships (SAR)
  - Qualitative: Activity cliffs, matched molecular pair analysis…
  - Quantitative: QSAR models
- 3-dimensional (3D) structure-based design
  - Scoring/affinity prediction
  - Understanding 3D SAR
- Linking 2D and 3D SAR to guide design
- Conclusions

2D Structure-Activity Relationships

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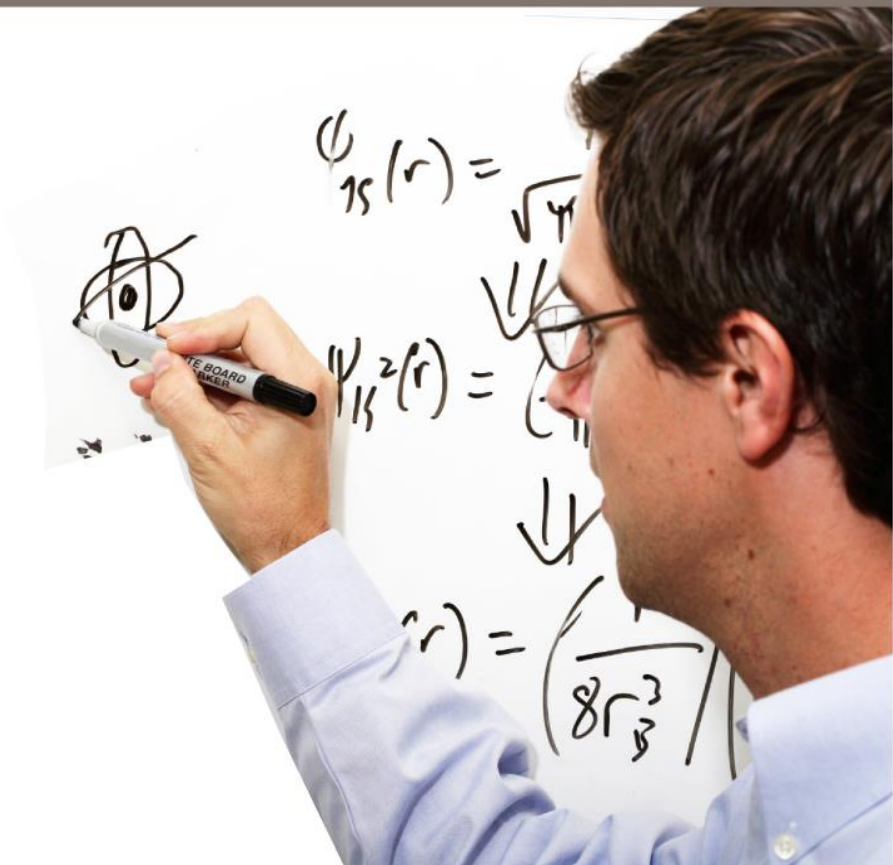


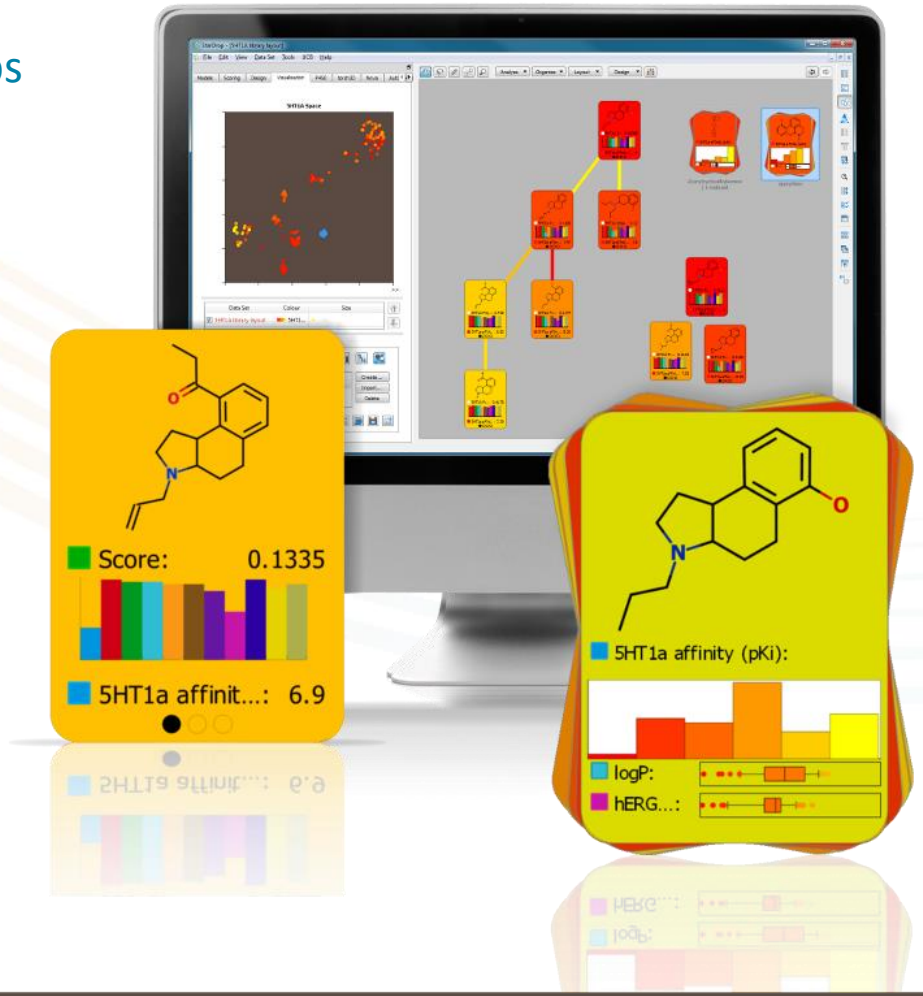
Qualitative SAR

Many methods are routinely used for analysis of data to reveal patterns and trends to guide compound optimisation, e.g.

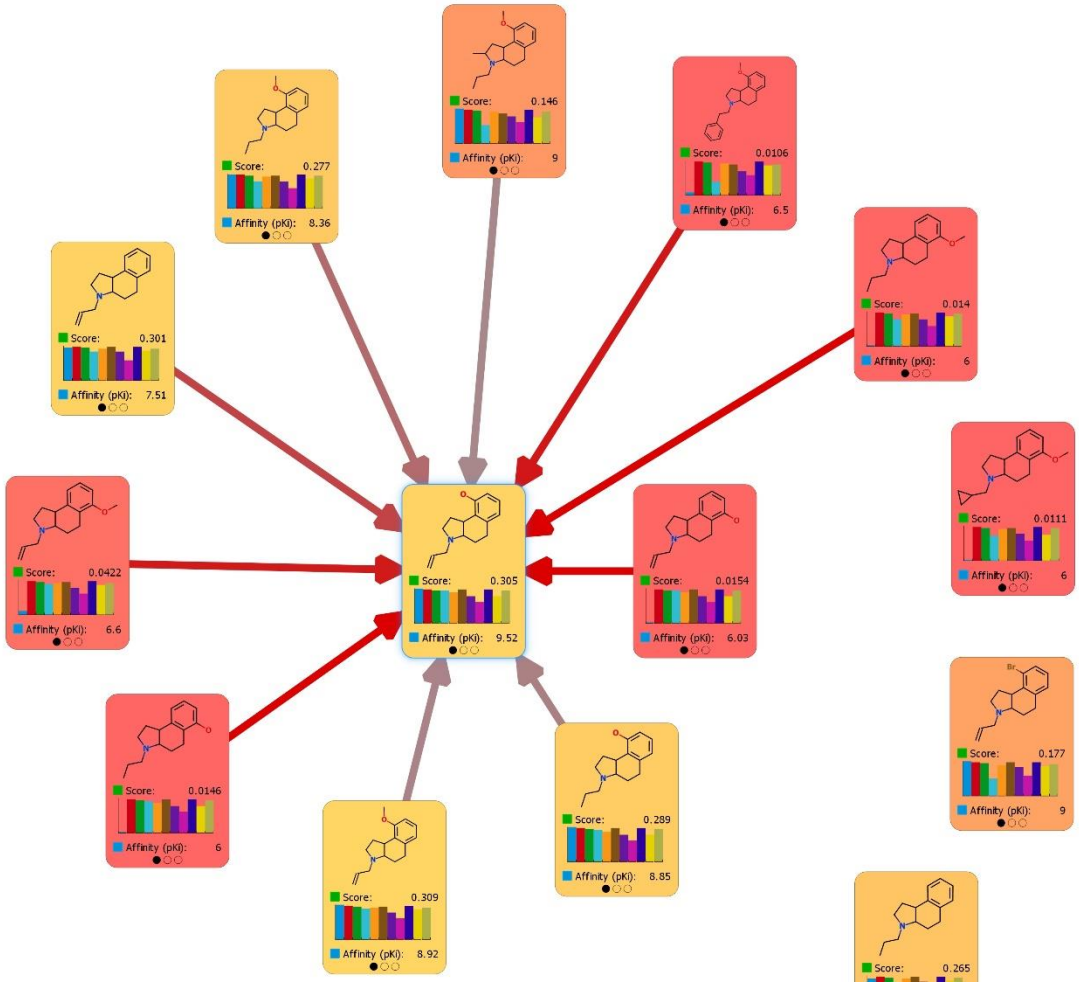
- Clustering
  - Group ‘similar’ compounds to identify series with interesting SAR
- Activity cliff detection
  - Small changes in structure that cause a large change in activity
- Matched molecular pair analysis
  - Pairs of compounds that are identical except for one small change at the same position

Visualising 2D SAR
Card View™

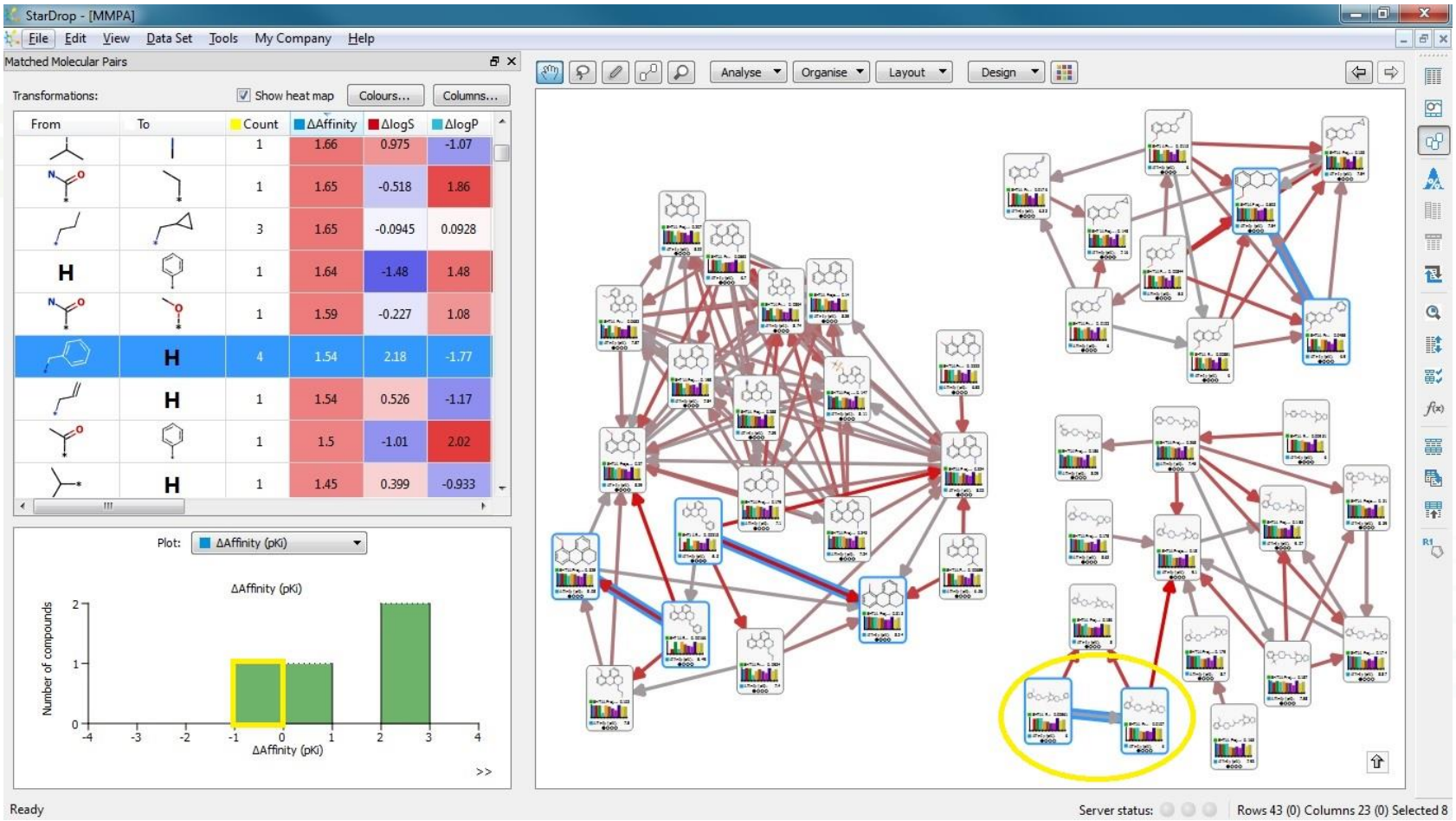
- Freedom from the constraints of ‘chemical spreadsheets’
  - Represent compound relationships
- Work the way you think
  - Cards: Display key compound data
  - Stacks: Summarise and compare data for groups of compounds
  - Links: Highlight compound relationships
- Intuitive visualisation of analyses
  - Clustering, activity cliffs, matched molecular pairs…
- Quickly identify optimisation strategies



Activity Neighbourhood
Activity Cliff Visualisation



Matched Molecular Pair Analysis



M.D. Segall *et al.* (2015) Drug Discov. Today **20**(9) pp. 1093-1103

Quantitative Structure-Activity Relationships
Principles

$$y = f(x_1, x_2, x_3, \ldots) \pm \varepsilon$$

Statistical uncertainty

- Data
  - Quality data is essential
  - Public data needs very careful curation (and may not be good enough)
- Descriptors, e.g.
  - Whole molecule properties, e.g. logP, MW, PSA…
  - Structural descriptors, SMARTS, fingerprints…
- Statistical fitting or machine learning method, e.g.
  - Partial least squares, artificial neural networks, support vector machines, random forest, Gaussian processes…
- Widely applied to prediction of ADME and physicochemical properties

Please see talk: COMP Wed. 8.40am Room 25C

Multi-Parameter Optimisation
Probabilistic Scoring

Integrated assessment of data against project criteria

Accounts for the uncertainties in all compound-related data (experimental or calculated)

Project specific scoring profile

Profile: 5HT1a Scoring Profile *

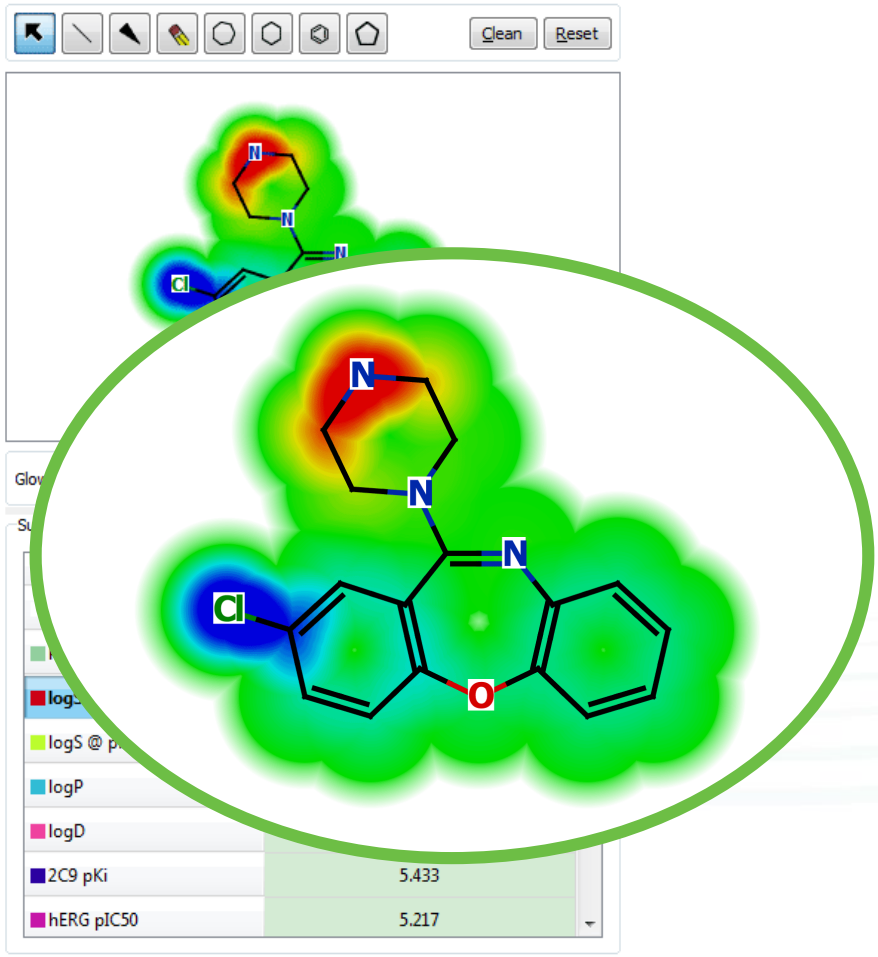
Property	Desired Value	Importance
pKi 5HT1a affinity	8.00 -> inf	
logS	> 1	
HIA category	+	
logP	0.0 -> 3.5	
BBB category	+	
BBB log([brain]:[blood])	-0.20 -> 1.00	
P-gp category	no	
hERG pIC50	⩽ 5	
2C9 pKi	⩽ 6	
2D6 affinity category	low medium	
PPB category	low	

Compounds ranked by likelihood of success

Histograms for quick visual guide to compound properties

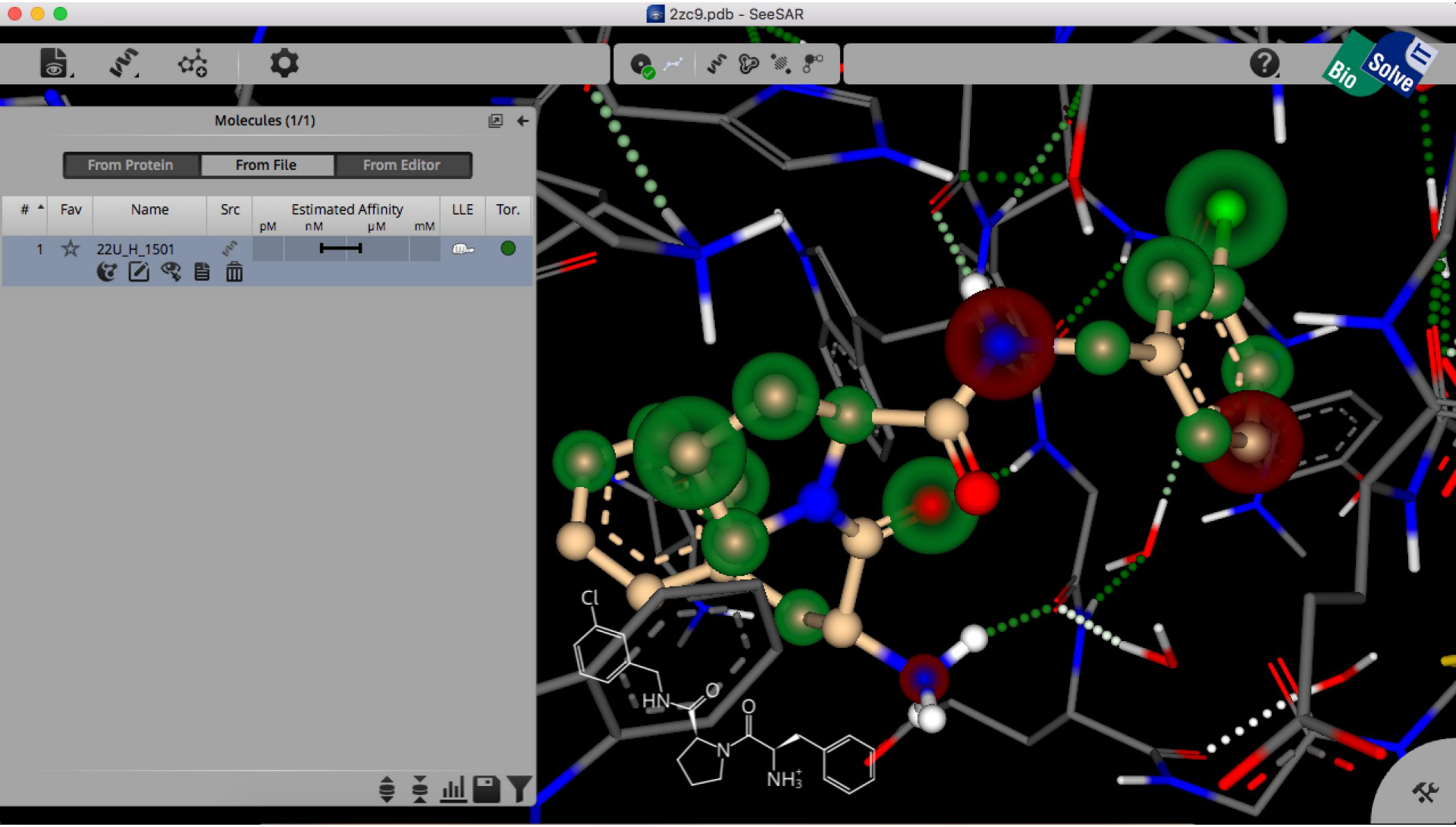
Interactive Redesign

- QSAR models provide estimates of compounds' properties
- Instant feedback on how properties are likely to change
  - Explore strategies for redesign
- But, important questions
  - "Why is a property value predicted?"
  - "Where can I change this property?"
- Glowing Molecule™:
  - Visual indication of structural influences on predicted properties

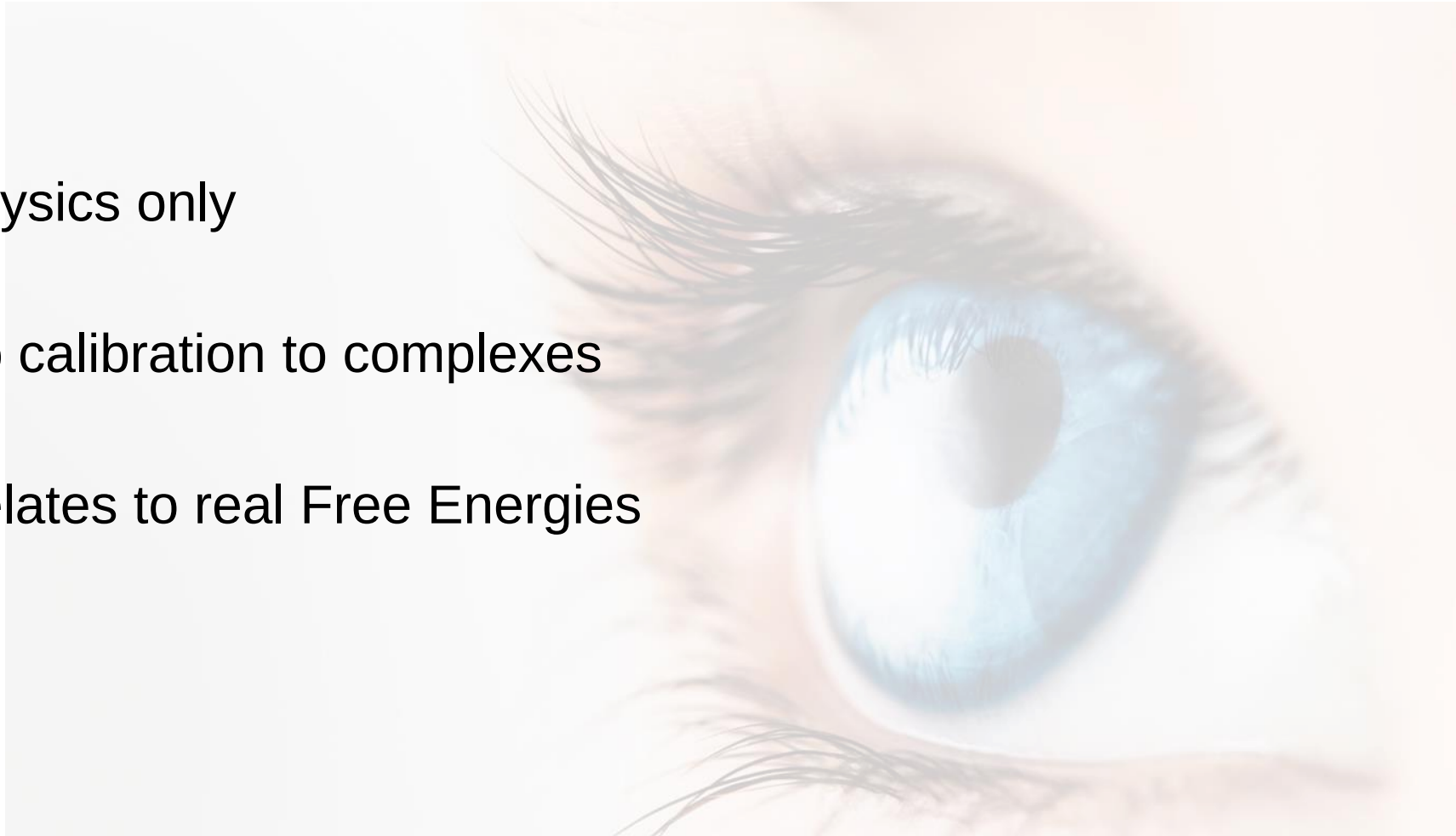


3D Structure-Based Design

Visual Understanding of 3D Affinity Data



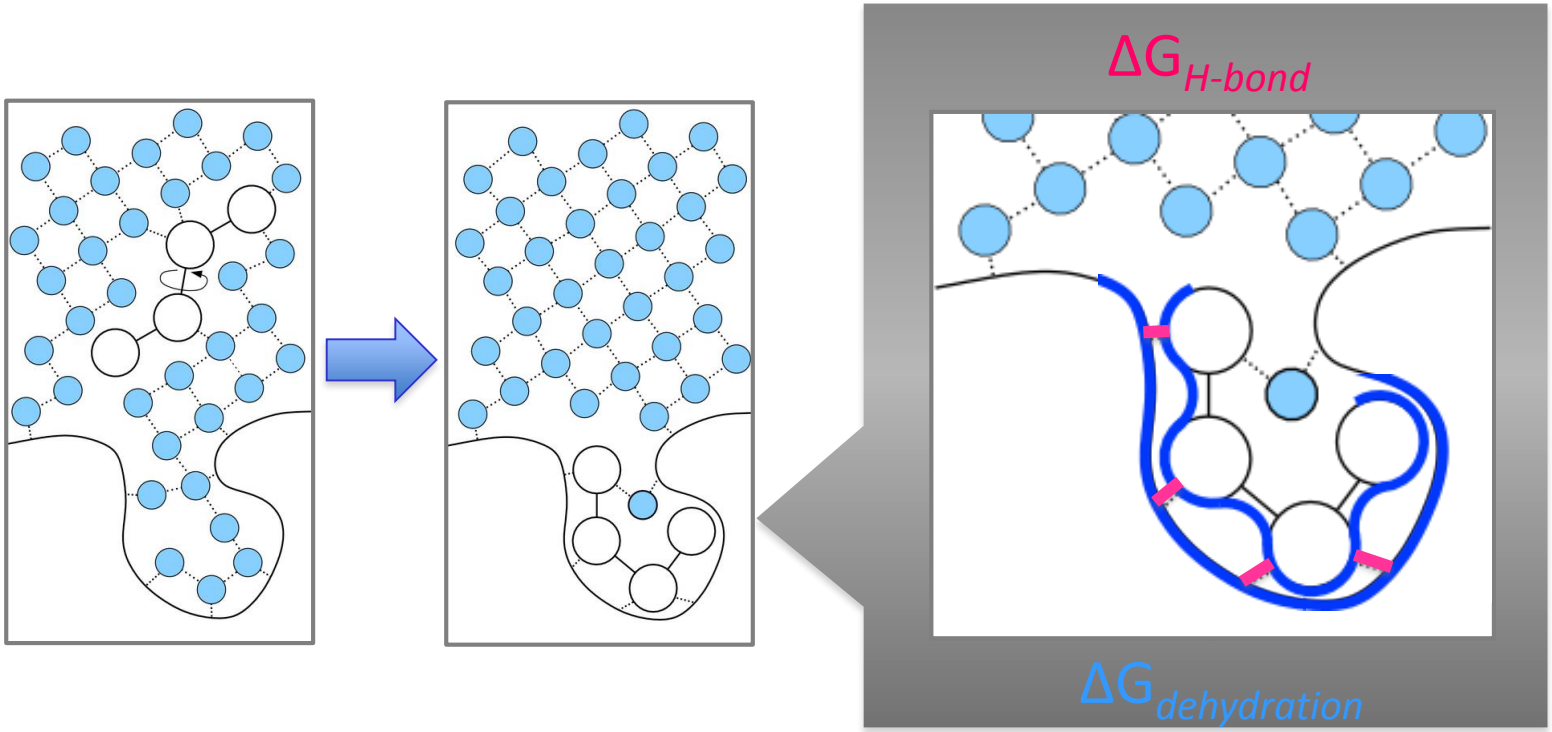
HYDE: A Different View @ Energetics*



- Physics only
- No calibration to complexes
- Relates to real Free Energies

***CINF 9: Christian Lemmen, "Predicting binding affinity doesn't work, or does it?" Next talk!**

HYDE Scoring Function – Concept*



$$\Delta G^{i}_{\mathrm{HYDE}} = \sum_{atom\ i} \Delta G^{i}_{dehydration} + \Delta G^{i}_{H-bond}$$

*Reulecke et al., ChemMedChem'08

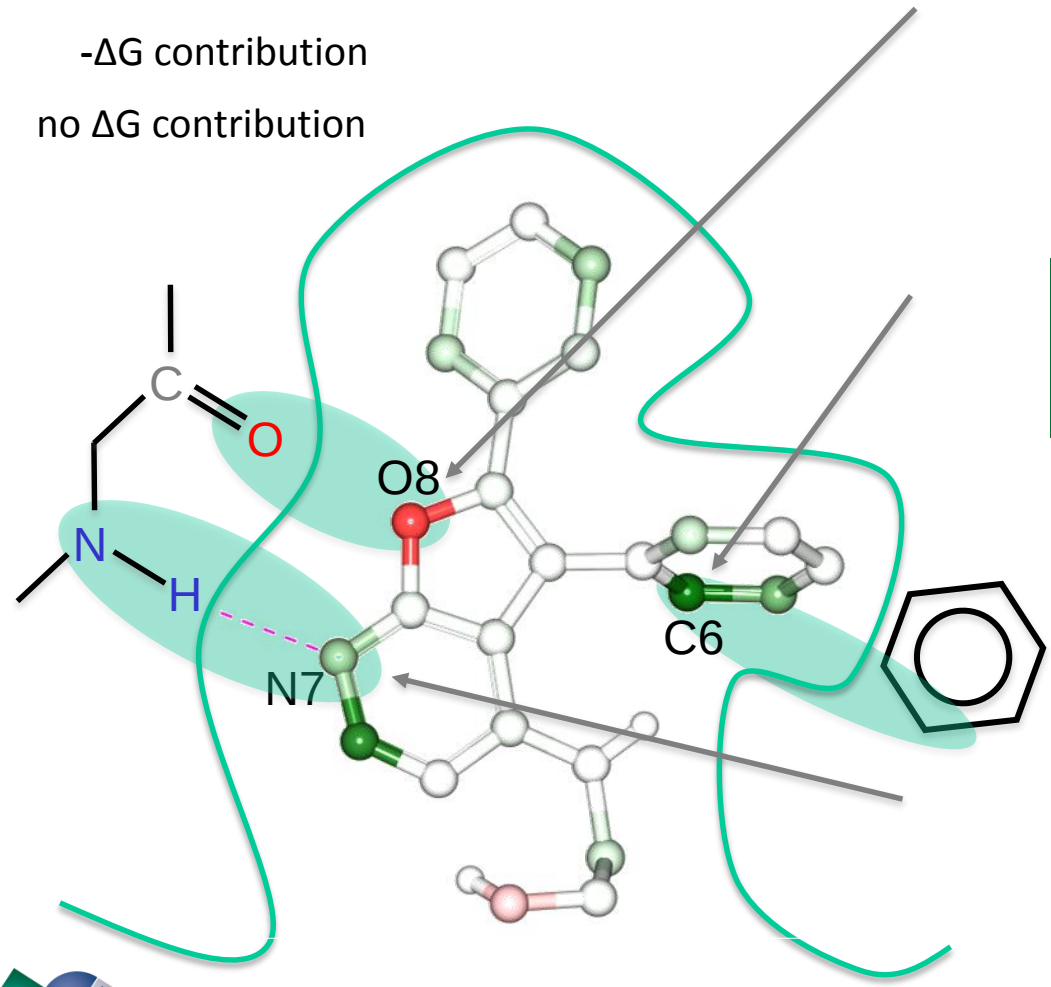
Hyde - Visual Affinities

HYDE color code:

+ΔG contribution

-ΔG contribution

no ΔG contribution

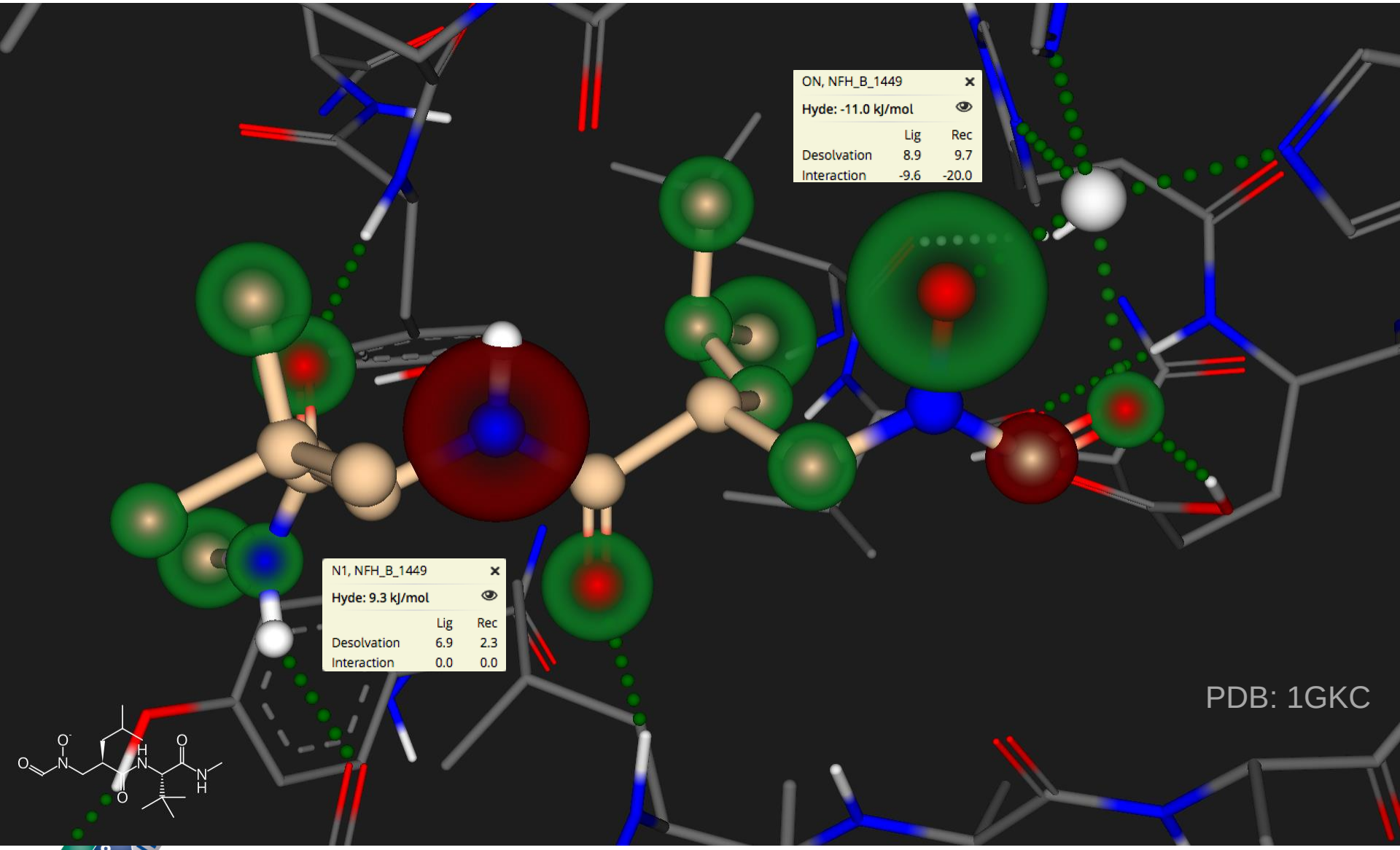


receptor carbonyl oxygen	8.2 kJ/mol
ligand aromatic oxygen	2.4 kJ/mol
total desolvation cost	**10.6 kJ/mol**

receptor aromatic carbons	-5.2 kJ/mol
ligand aromatic carbon	-2.0 kJ/mol
total desolvation gain	**-7.2 kJ/mol**

receptor amide N dehydrat	6.3 kJ/mol
interaction energy	-7.4 kJ/mol
ligand aromatic N dehydrat	6.4 kJ/mol
interaction energy	-7.5 kJ/mol
total H-bond energy	**-2.2 kJ/mol**

Visual Understanding of 3D Affinity Data



Linking 2D and 3D SAR to Guide Design

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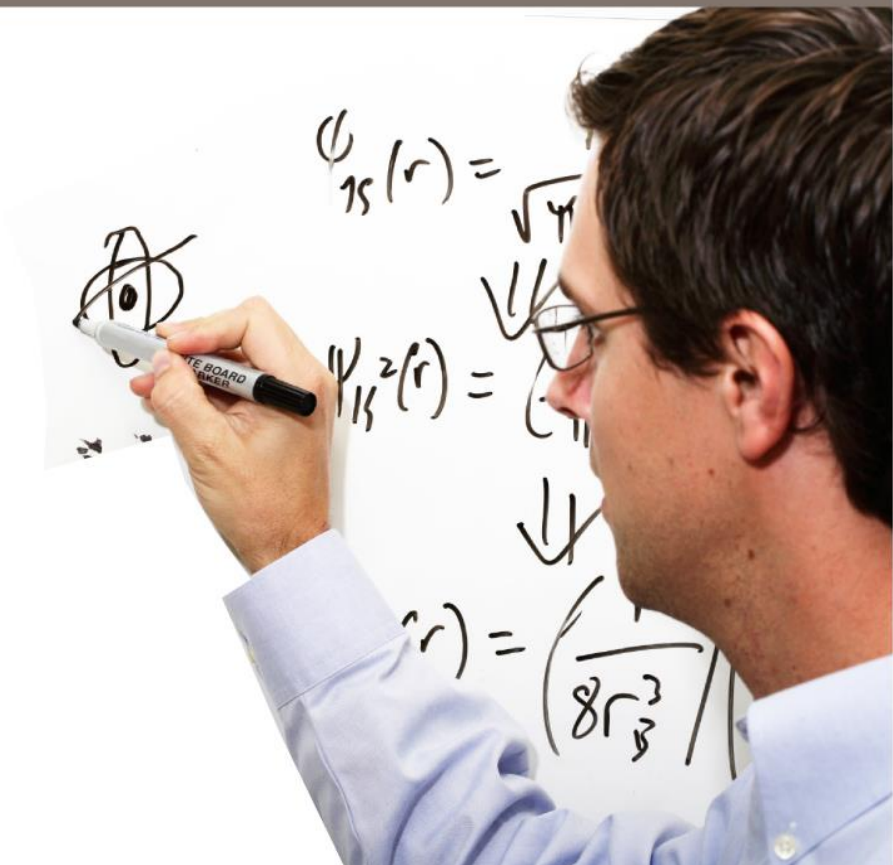
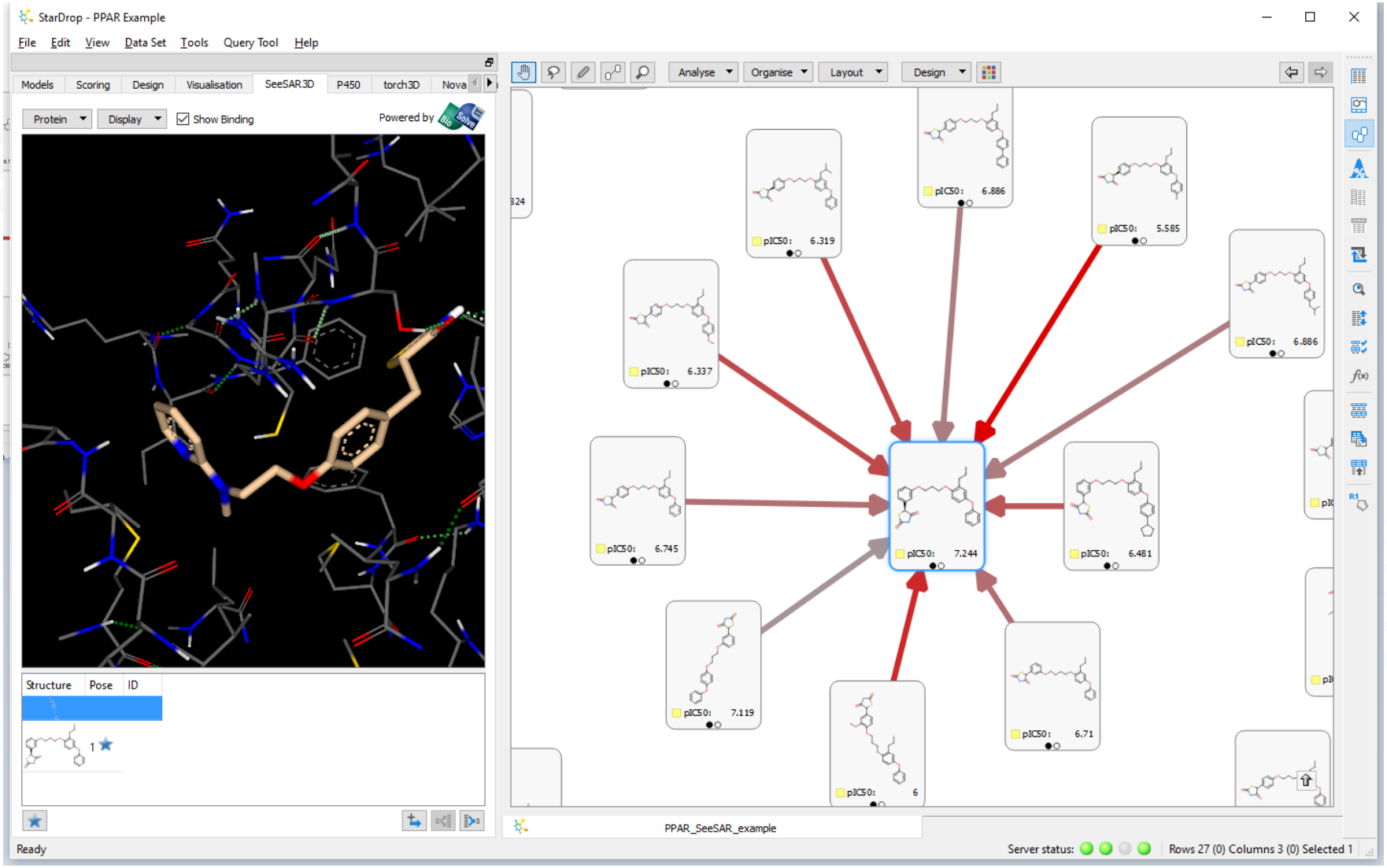


Understanding Activity Cliffs in 3D

PPAR$_\gamma$ PDB 4EMA



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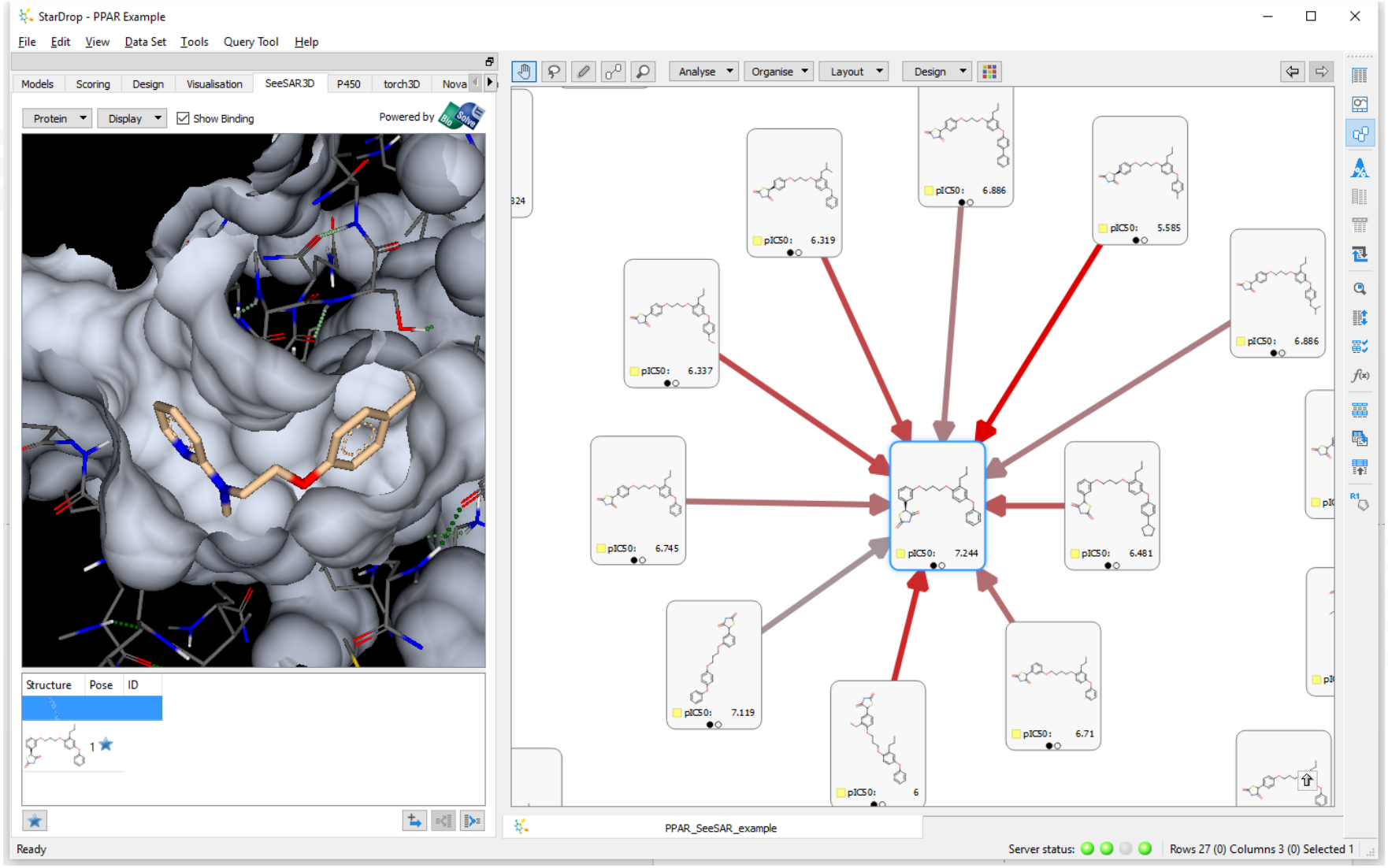

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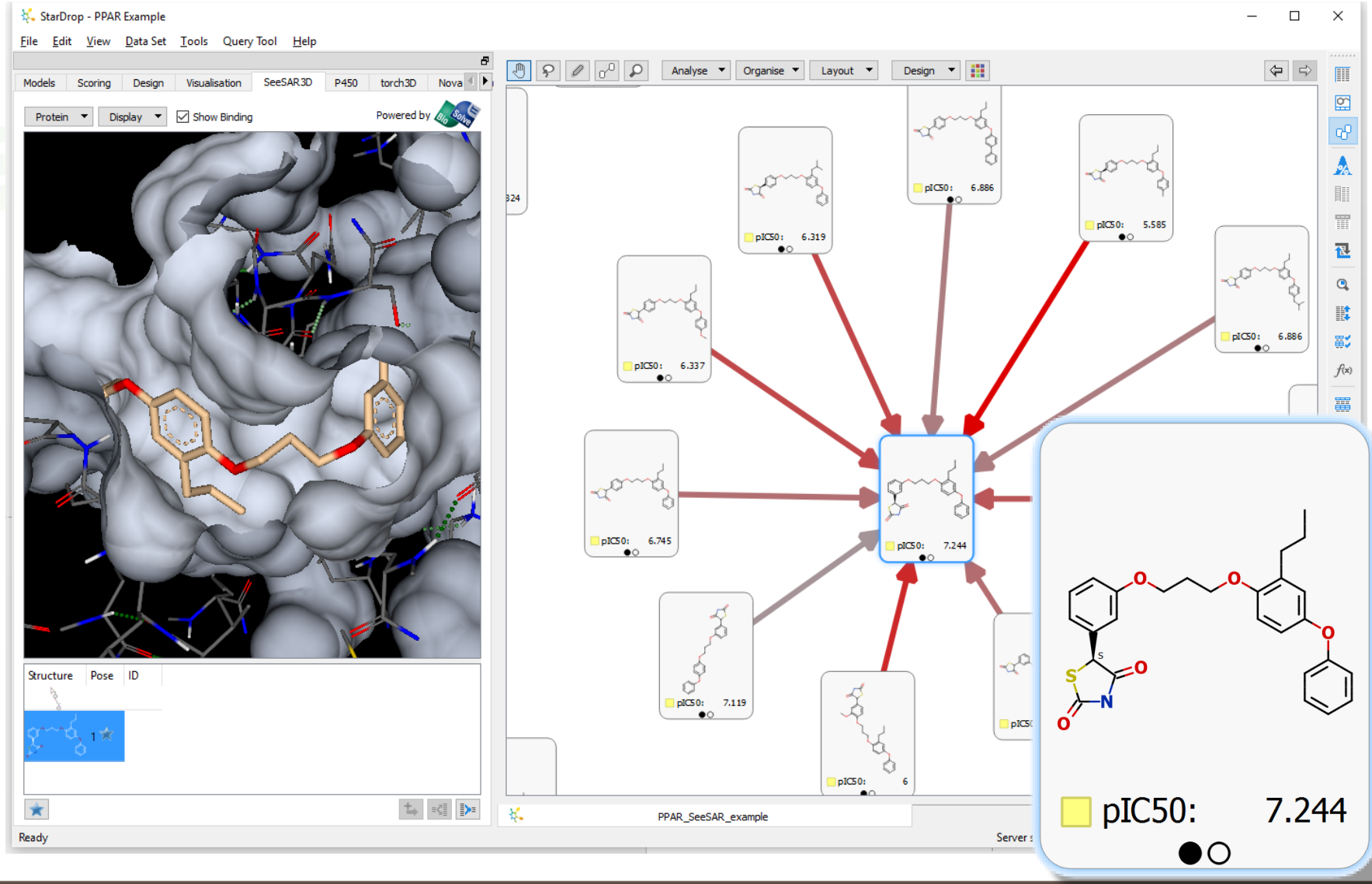

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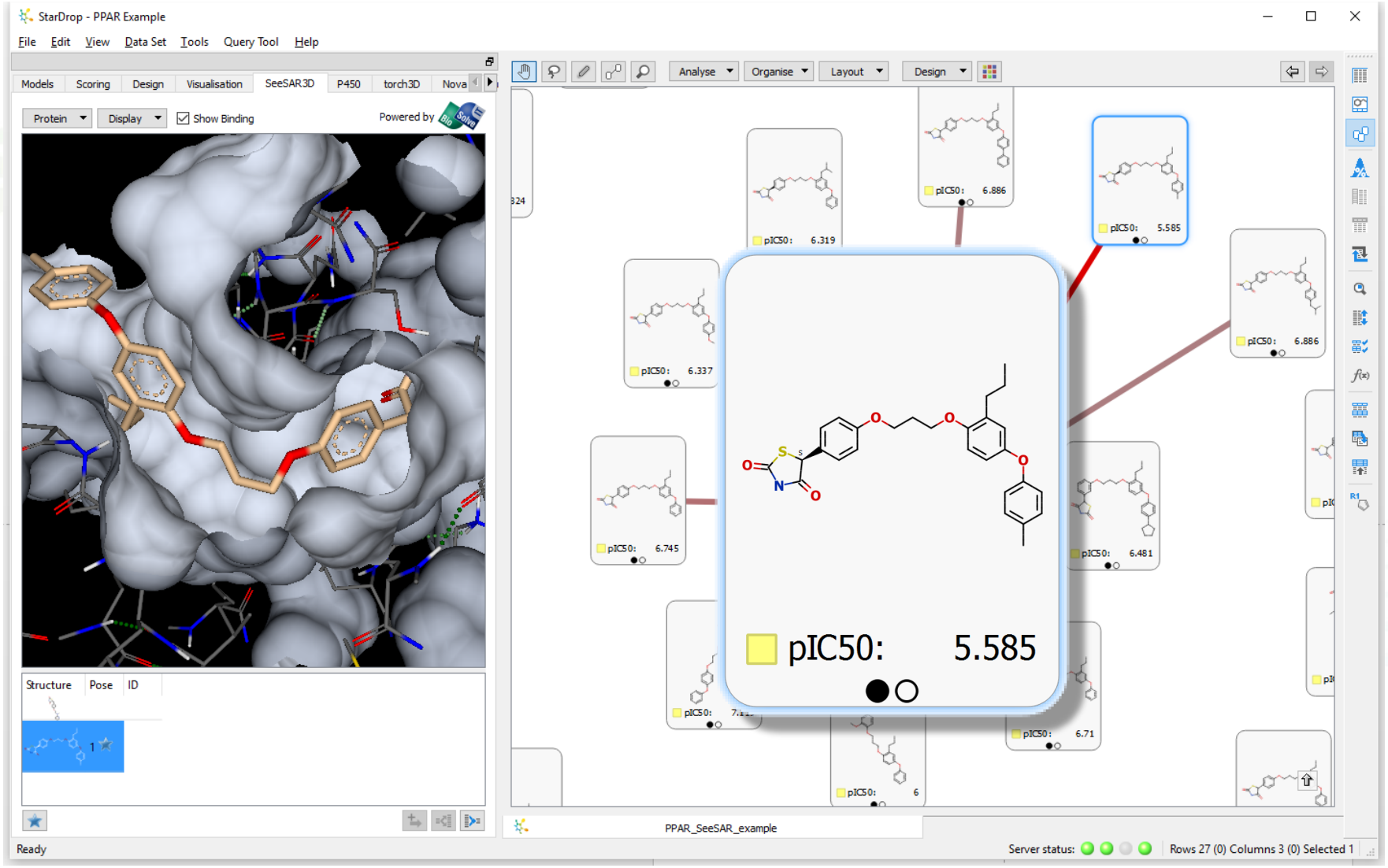

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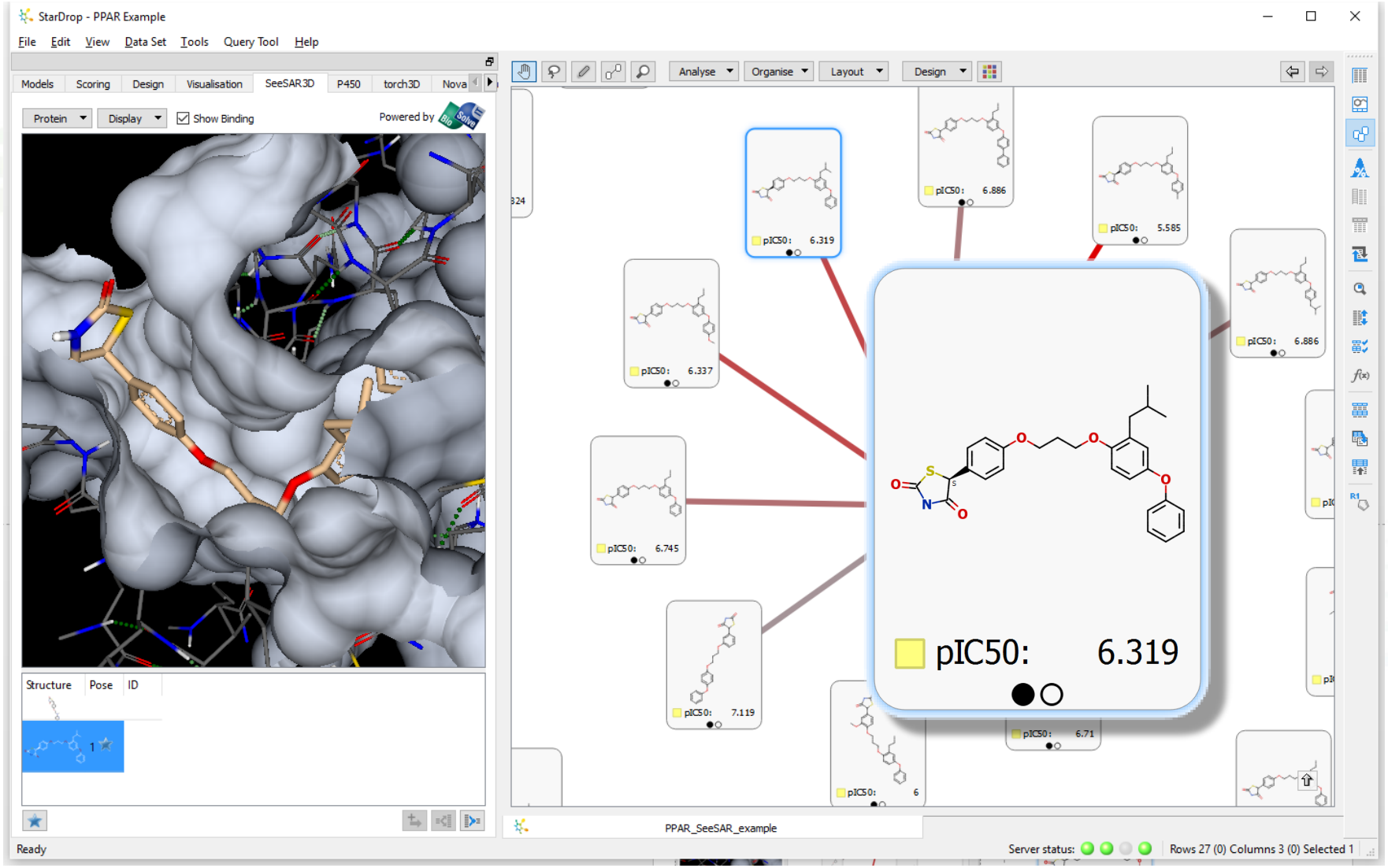
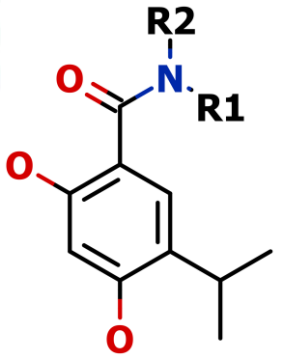
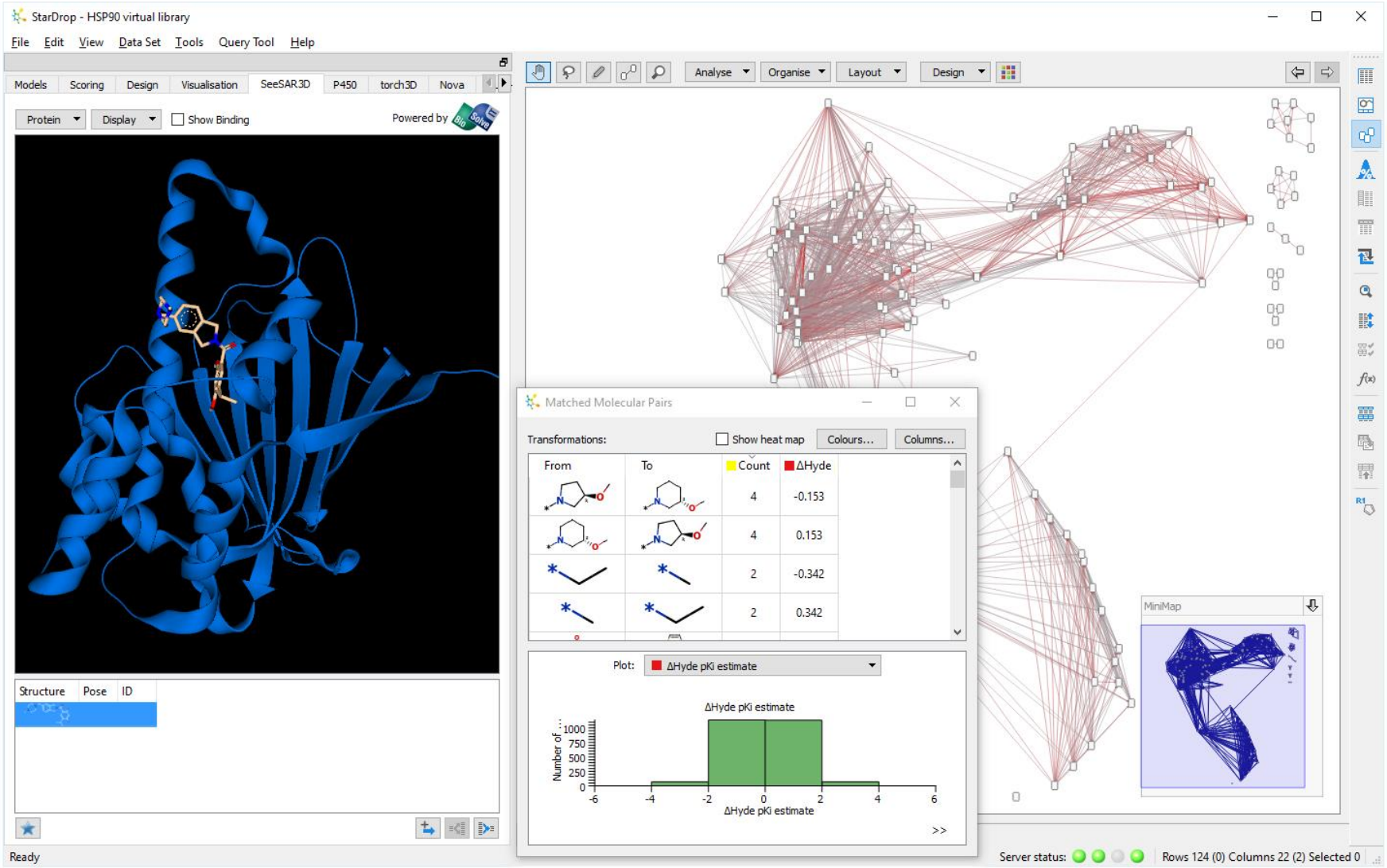


Exploration of Virtual Screening Results
HSP90

- Crystal structure PDB ref. 2XJX
- Virtual library generated using STORM workflow in KNIME
  - Amide substitution using Schotten Baumann reaction on beta resorcylic core
  - Building blocks from vendor catalogues
  - 'Tail' of molecule not contributing to affinity
- Resulting library docked with FlexX
- Scored using SeeSAR and HYDE to estimate pK_i



Matched Molecular Pair Analysis



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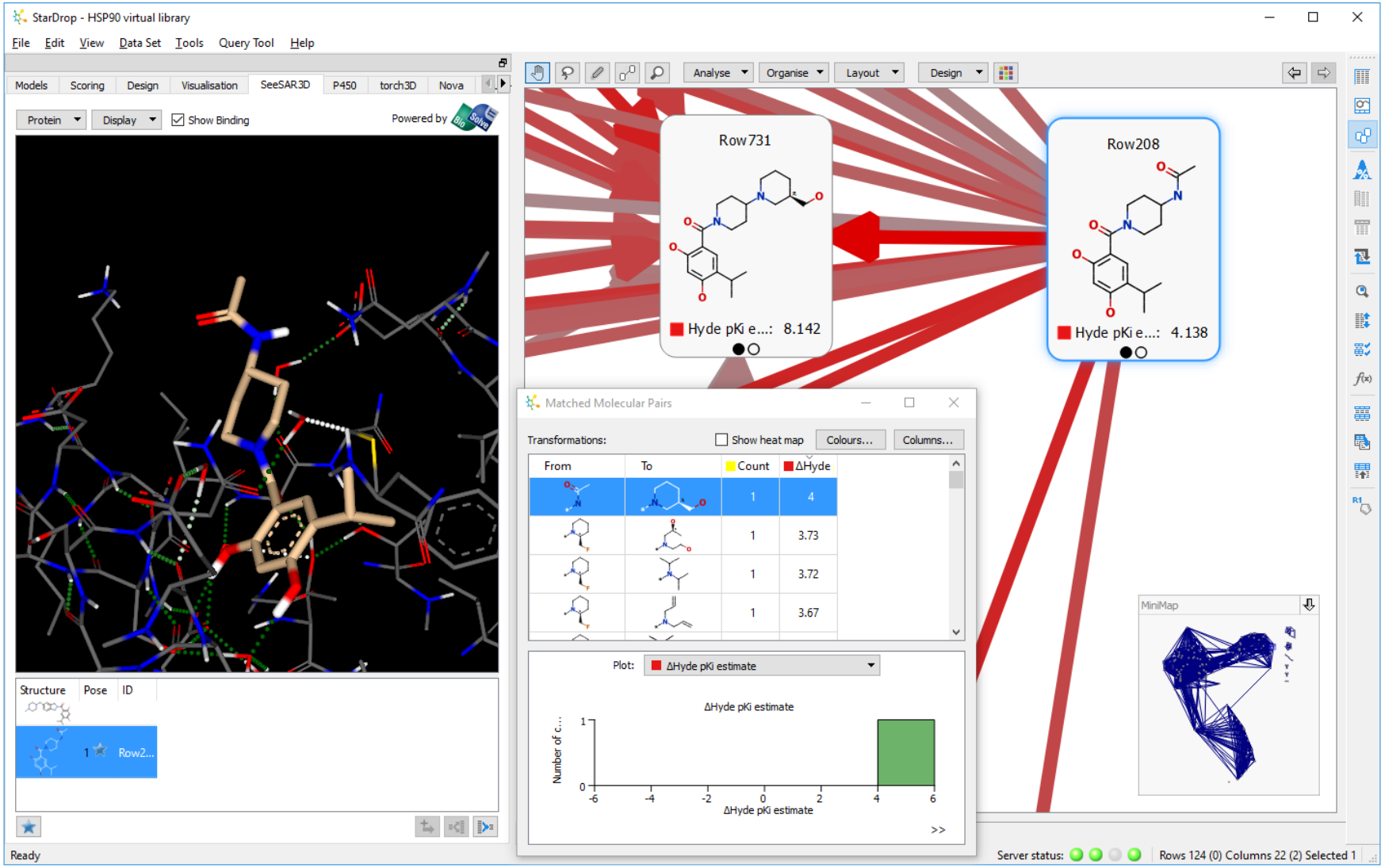

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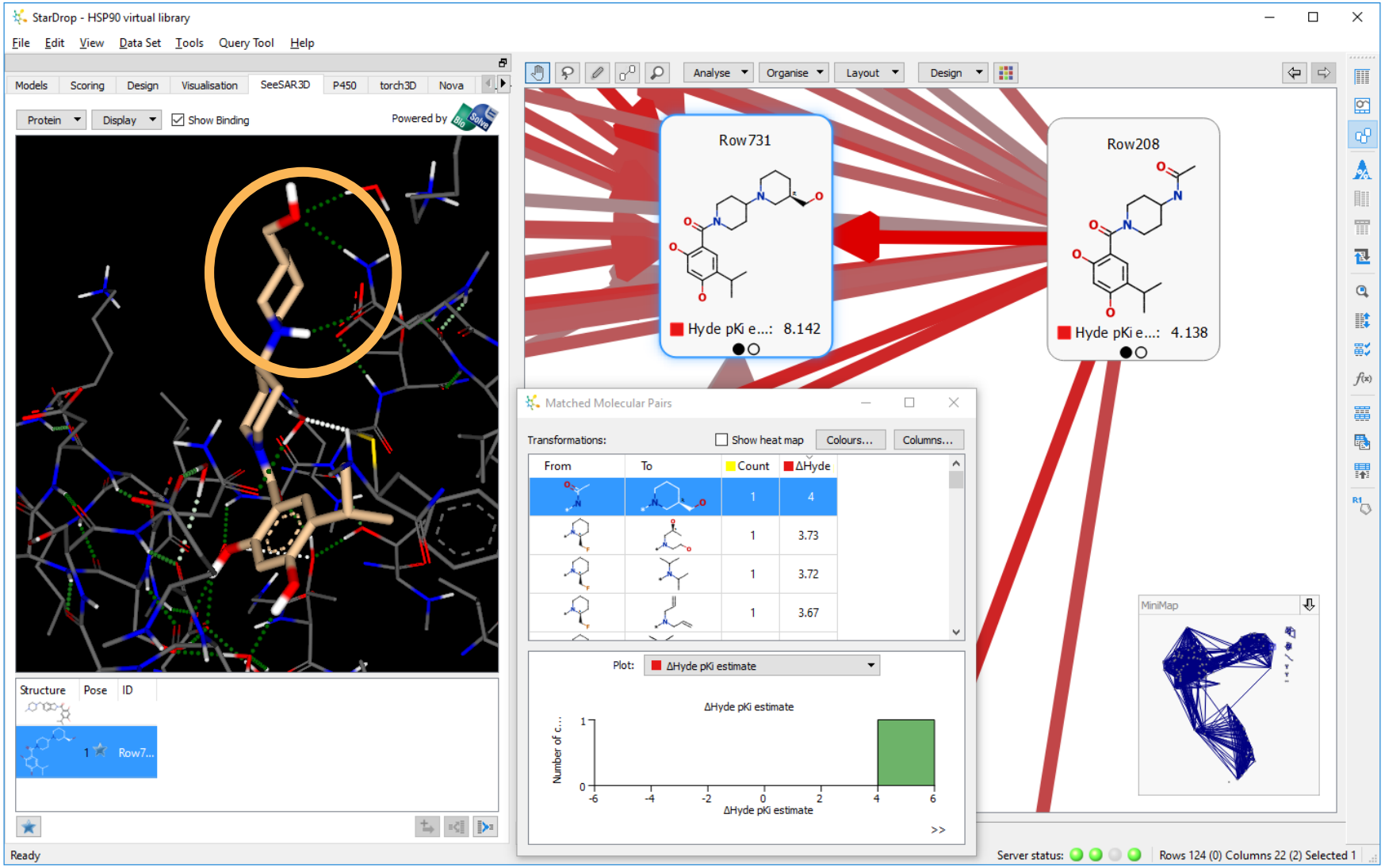

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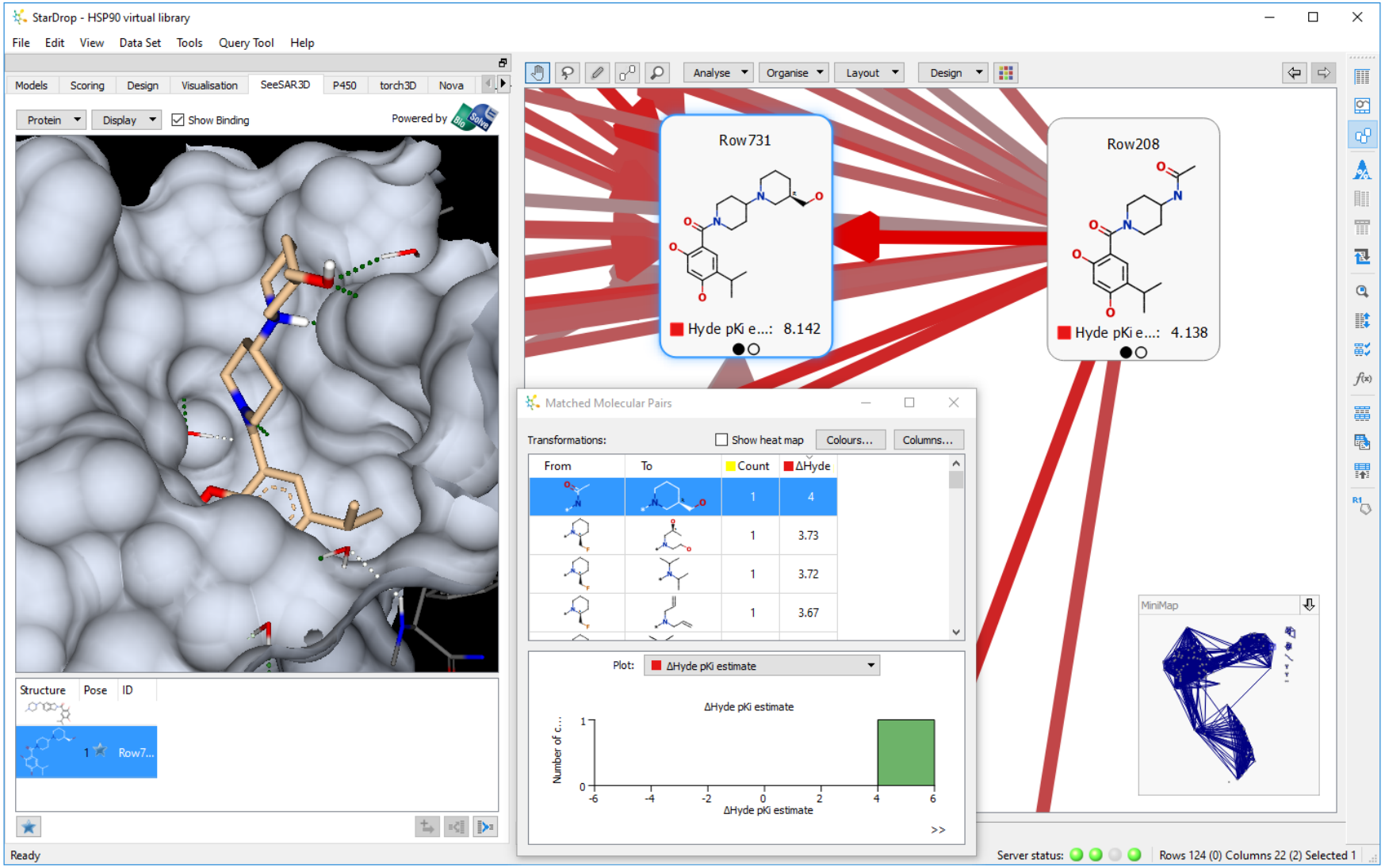
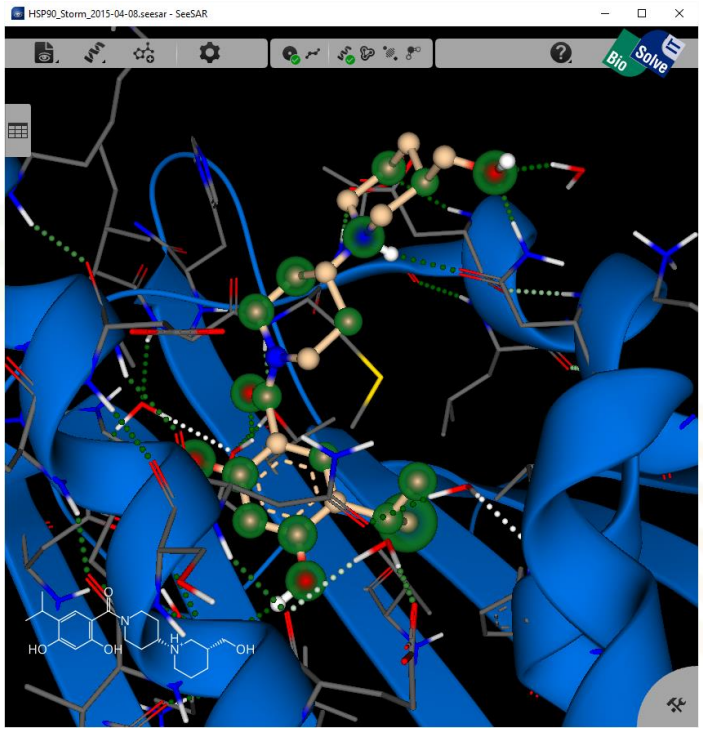
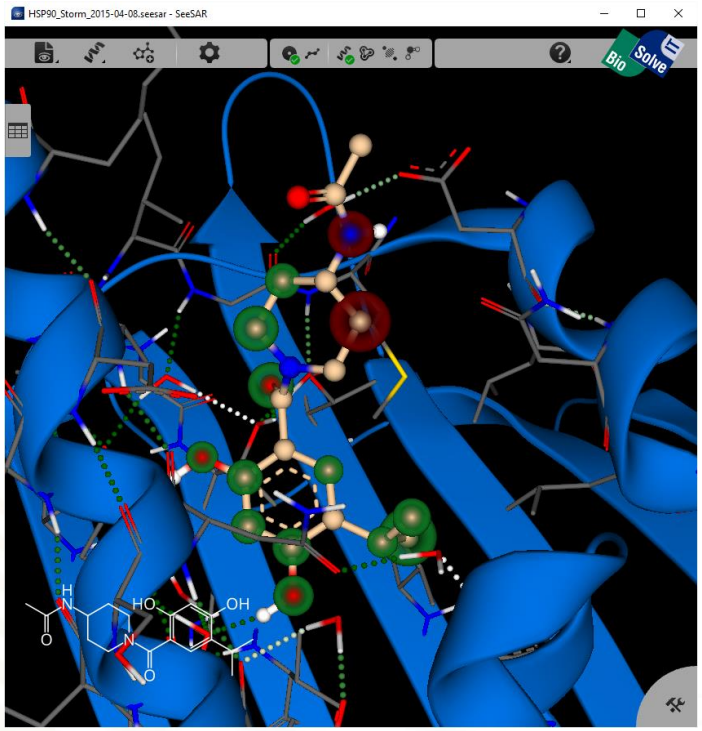
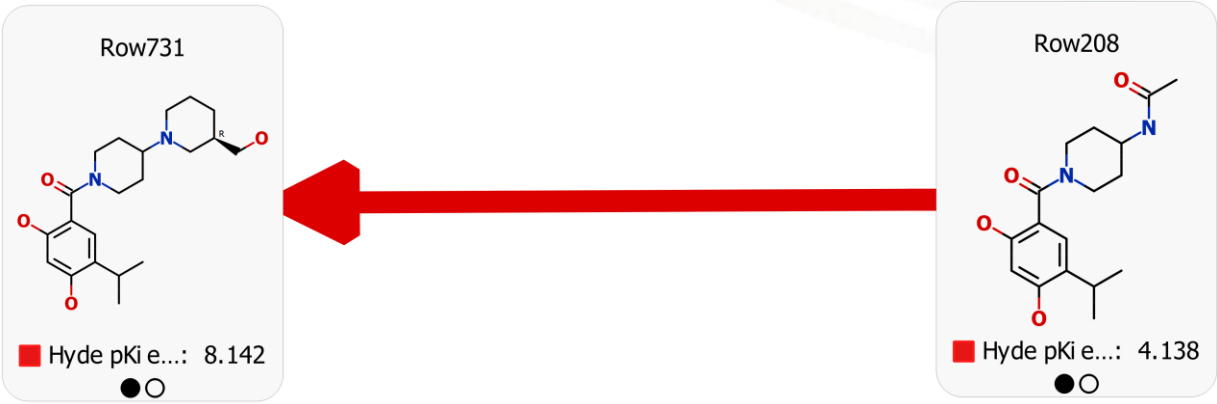


HYDE Analysis in SeeSAR

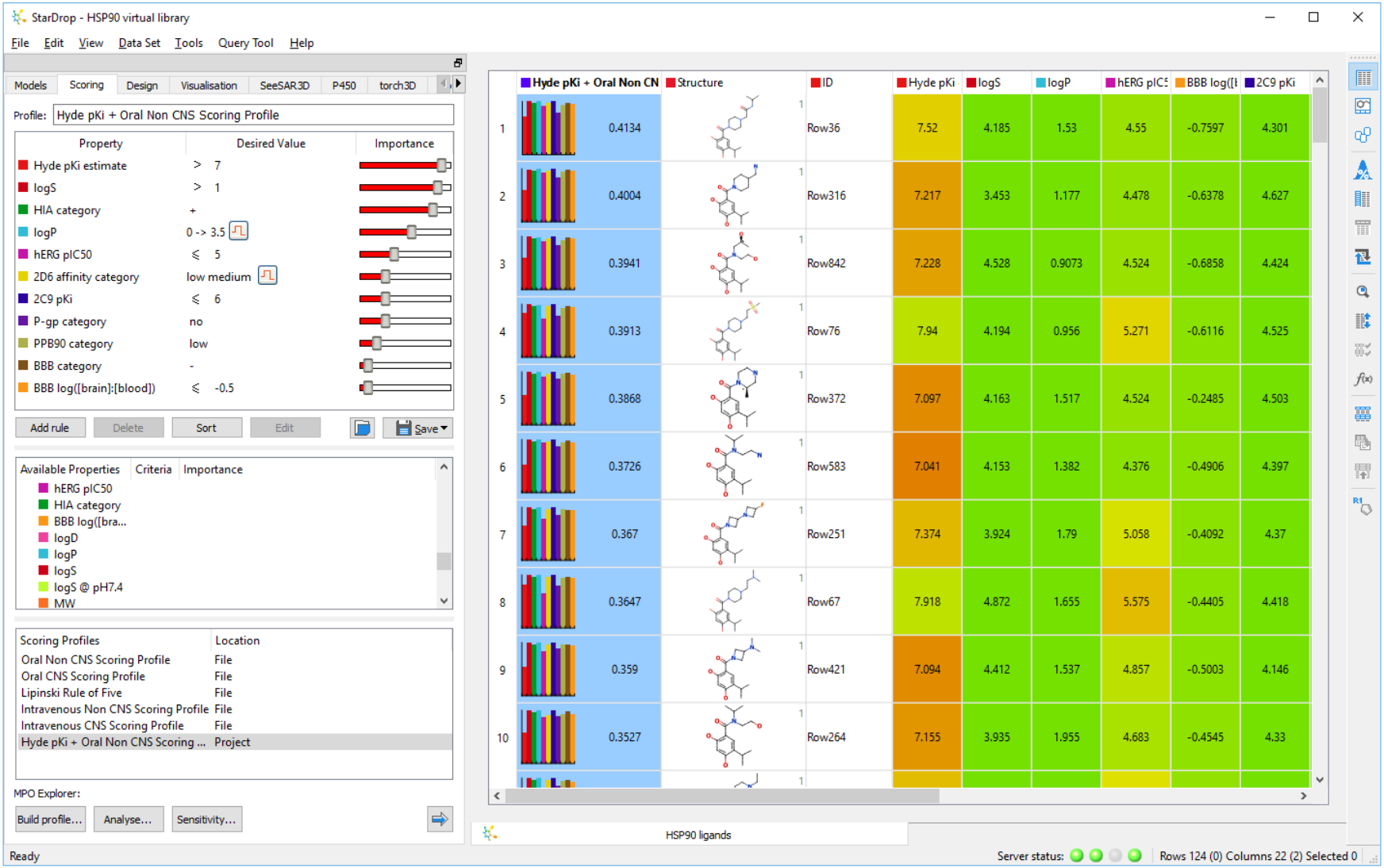




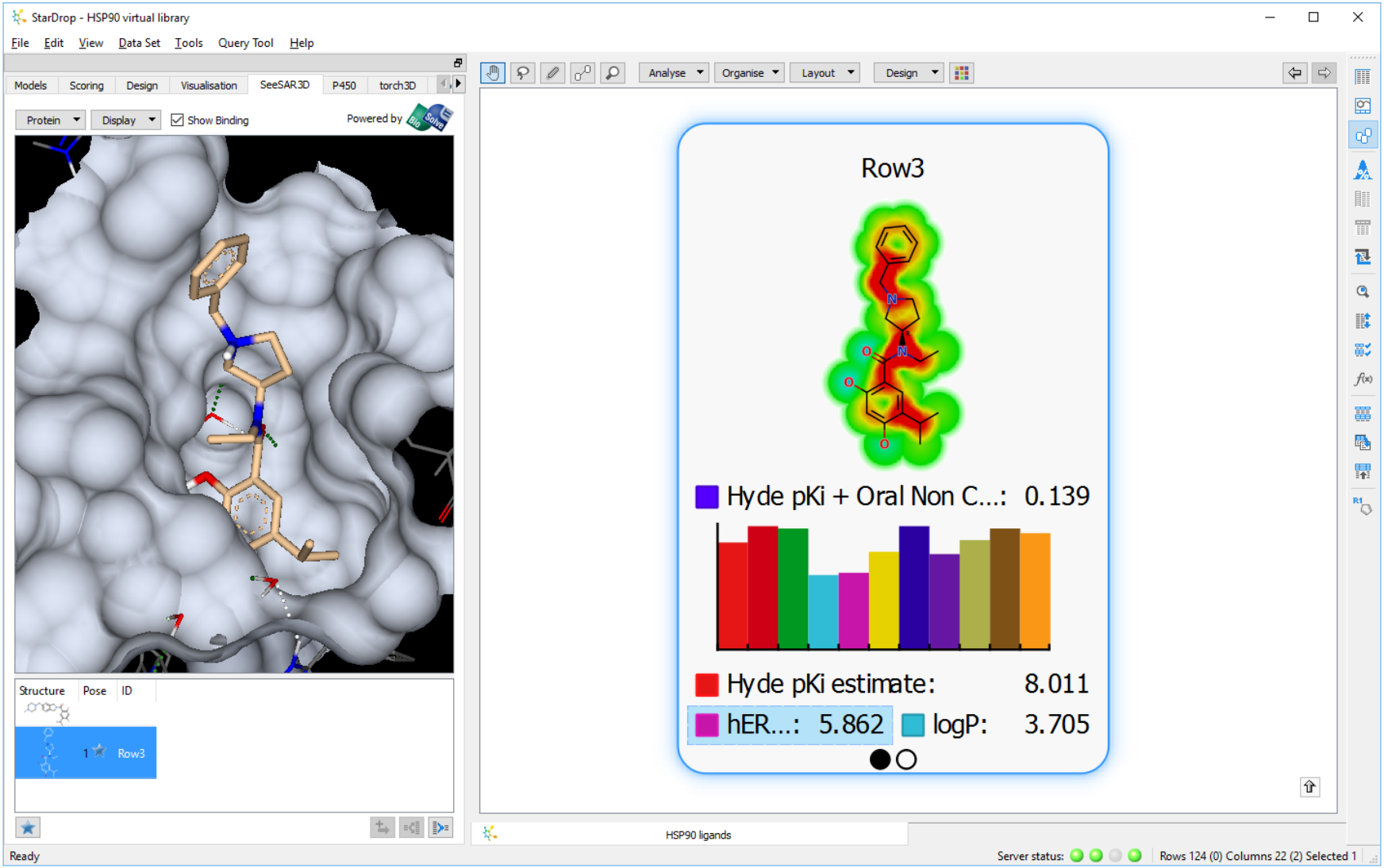


Combine with 2D QSAR Predictions

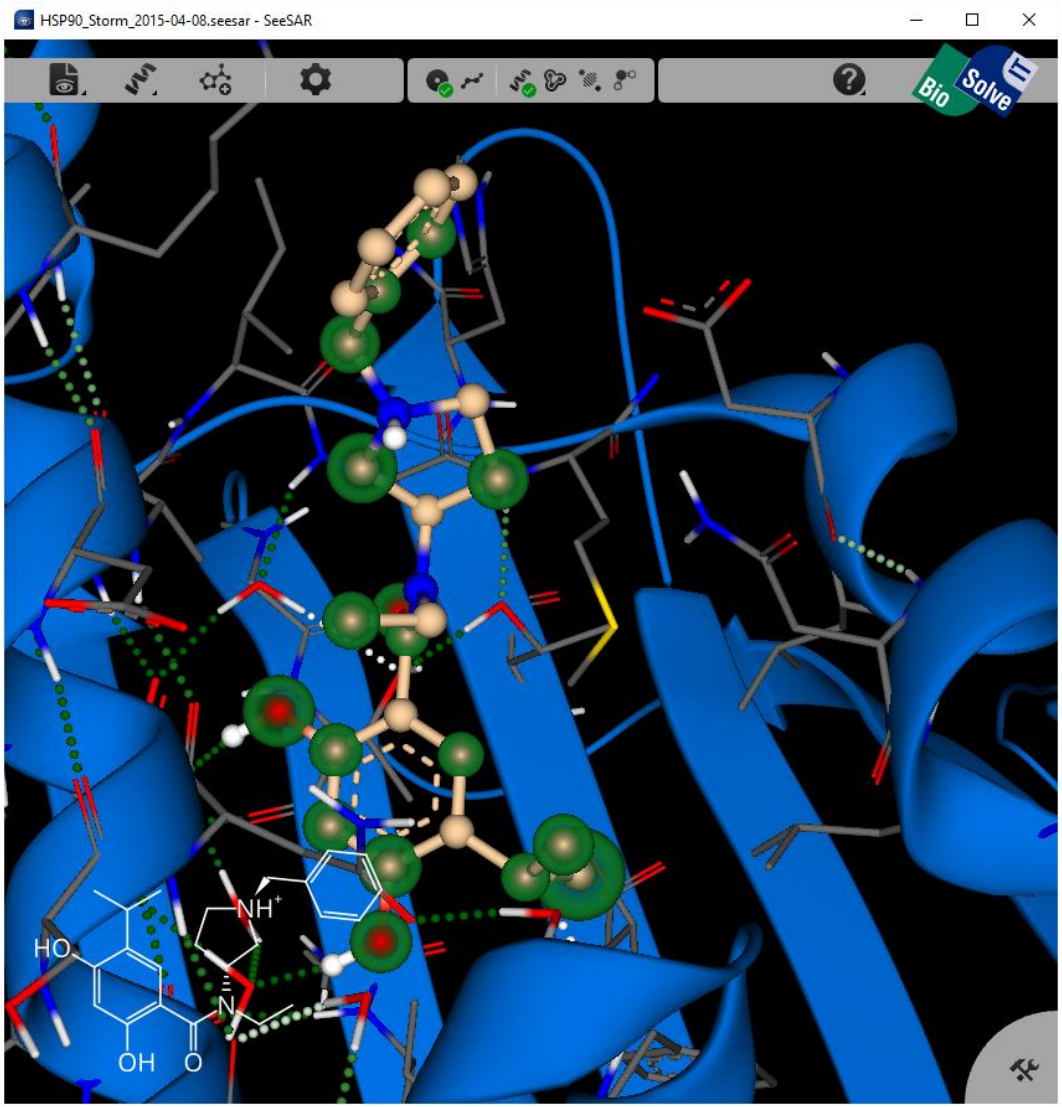
Multi-parameter optimisation



3D View… Optimisation opportunities

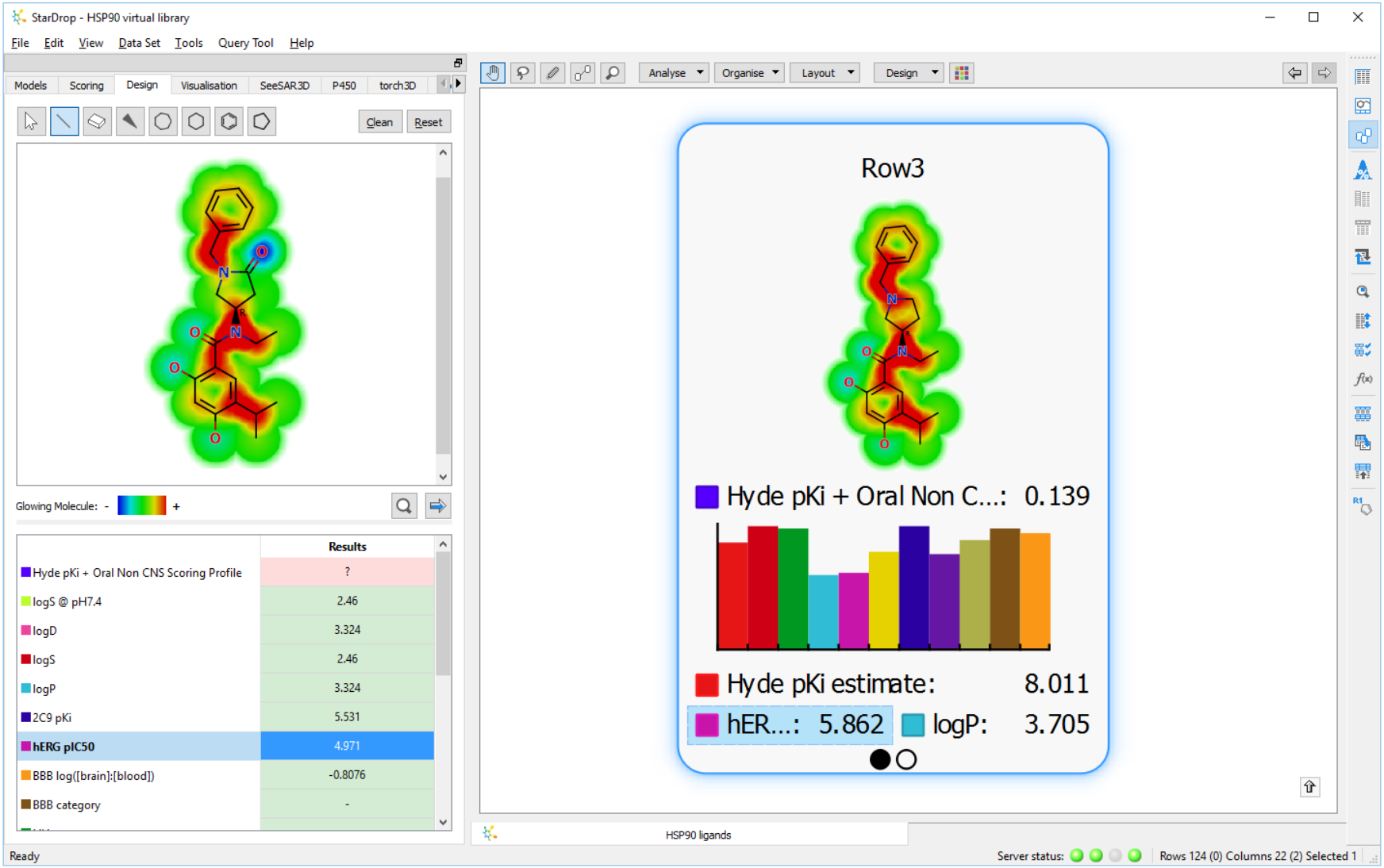


HYDE Analysis in SeeSAR



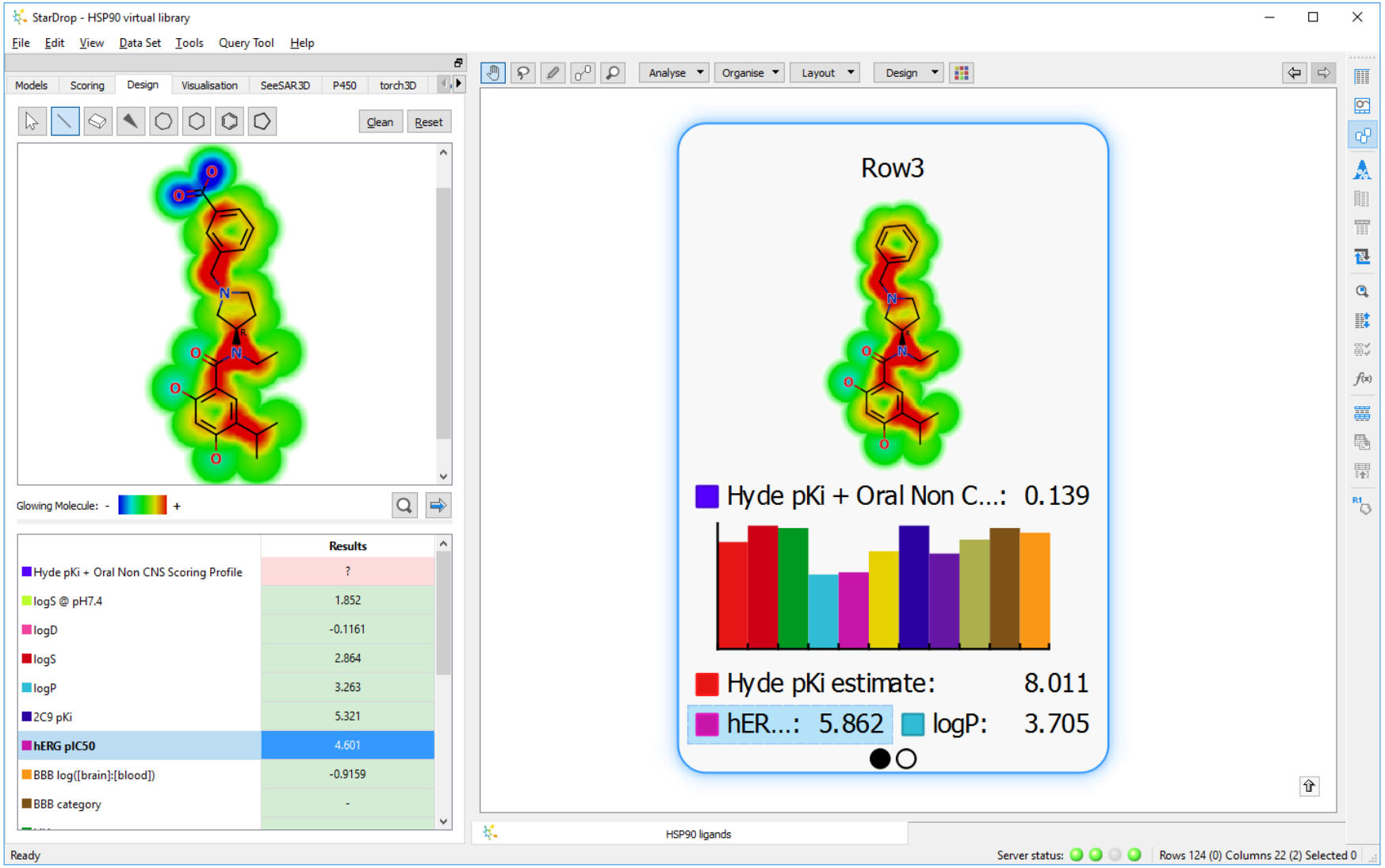
Optimisation Idea

Modify pKa of Nitrogen by amide substitution

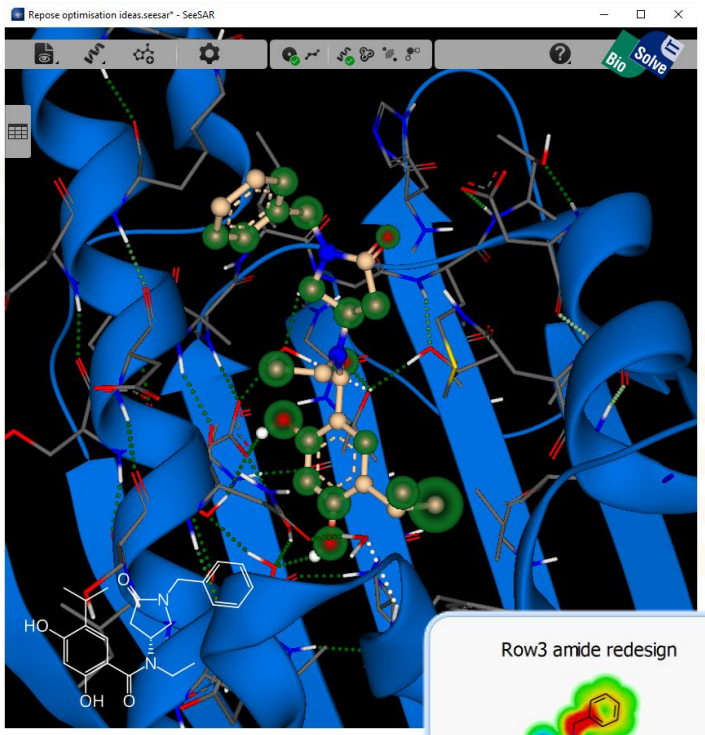


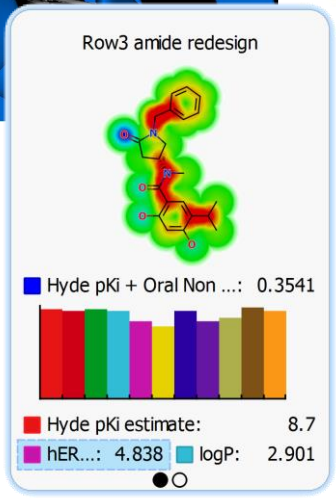
Optimisation Idea

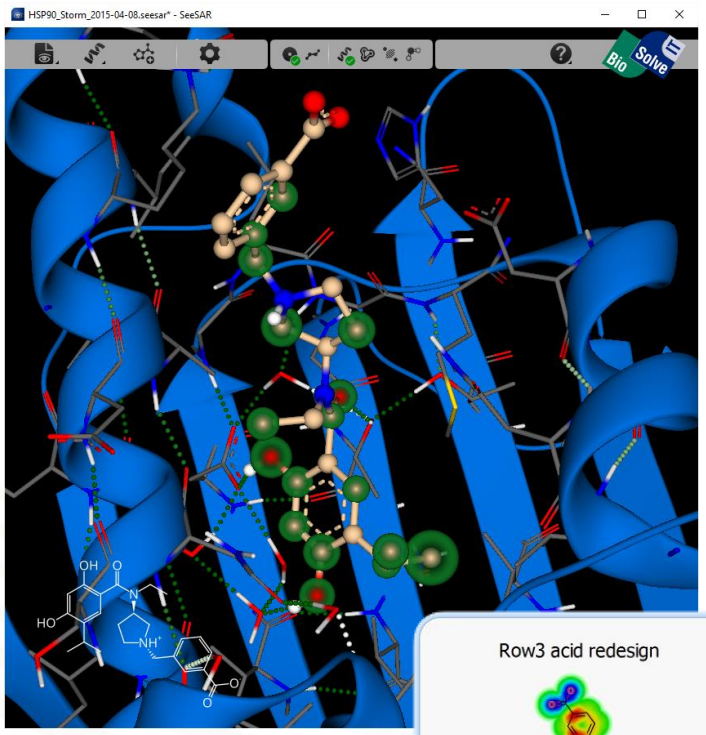
Add polar group to phenyl ring

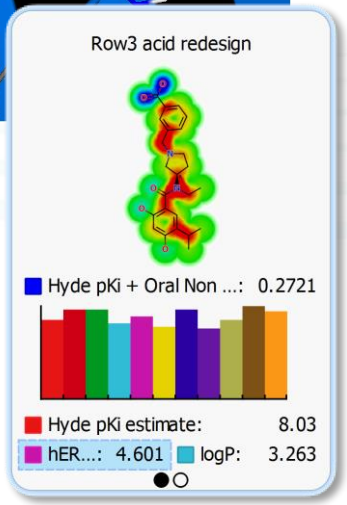


Repose in SeeSAR









Conclusions

- Both 2D and 3D information are important to interpret SAR and guide design
- A seamless combination between these two views of the chemical world maximises the benefits that they bring
  - Understanding SAR from experimental data
  - Analysis of virtual screening/docking results
  - Multi-parameter optimisation of potency, physicochemical and ADMET properties
- For more information:
  - www.optibrium.com/stardrop and www.biosolveit.com/SeeSAR
  - Optibrium: Booth 1227 or outside of room 6E (MEDI)

Free Hands-On Workshop

Seamless Integration of 2D and 3D SAR to Guide MPO

- Where: San Diego Convention Center, Room 15B
- When: Monday 3:30pm to 6pm
- Practical examples with SeeSAR and StarDrop
- Spaces are limited, so please **register at Booth #1227** in the Exhibition Hall